**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION**
**DECISION SUMMARY**
**DEVICE ONLY TEMPLATE**

**A. 510(k) Number:**
k033606

**B. Analyte:**
B-type natriuretic peptide test system (BNP)

**C. Type of Test:**
Quantitative

**D. Applicant:**
Axis-Shield Diagnostics

**E. Proprietary and Established Names:**
Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA), Abbott AxSYM Standard Calibrators, Abbott AxSYM BNP Controls

**F. Regulatory Information:**

1. Regulation section:
   862.1117, B-type natriuretic peptide test system
   862.1150, Calibrator, Secondary
   862.1660, Single (specified) analyte controls (assayed and unassayed)
2. Classification:
   Class II, Class II, Class I
3. Product Code:
   NBC; JIT; JJX
4. Panel:
   75

**G. Intended Use:**

1. Indication(s) for use:
   AxSYM® BNP is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma on the AxSYM System. BNP values are used as an aid in the diagnosis and assessment of severity of heart failure.
2. Special condition for use statement(s):

3. Special instrument Requirements:
   Abbott AxSYM System

**H. Device Description:**
AxSYM BNP Reagent Pack (100 tests) consists of: 1 Bottle (8.4 mL) Anti-BNP (Mouse, Monoclonal) Coated Microparticles in TRIS Buffer (Reagent Bottle 1); 1 Bottle (13.2 mL) Anti-BNP (Mouse, Monoclonal) Alkaline Phosphatase Conjugate in TRIS buffer with protein stabilizers (Reagent Bottle 2); and 1 Bottle (14.1 mL) Wash Buffer containing detergent (Reagent Bottle 3).

AxSYM BNP Standard Calibrators consist of 6 Bottles (4 mL each) of AxSYM BNP Standard Calibrators. Calibrator A (0 pg/mL) is Acetate buffer with protein (Bovine) stabilizers. Calibrators B-F contain BNP in Acetate buffer with protein (Bovine) stabilizers to yield concentrations of 100 – 4000 pg/mL.

AxSYM BNP Controls consist of 3 Bottles (8 mL each) of AxSYM BNP Controls containing BNP in Acetate buffer with protein (Bovine) stabilizers to yield concentrations of approximately 100 – 1500 pg/mL.

**I. Substantial Equivalence Information:**

1. Predicate device name(s):
   Triage® B-Type Natriuretic Peptide (BNP) test
2. Predicate K number(s):
   K021317
3. Comparison with predicate:

| Similarities | | |
|---|---|---|
| **Item** | **Abbott AxSYM BNP** | **Triage® BNP** |
| Intended Use | Similar | Similar |
| Type of test | Quantitative | Quantitative |
| End point | Fluorescent | Fluorescent |
| **Differences** | | |
| **Item** | **Abbott AxSYM BNP** | **Triage® BNP** |
| Analyzer | Abbott AxSYM System | Biosite Triage® Meter |
| Technology format | Automated sandwich format Microparticle enzyme immunoassay | Single use device, sandwich format, fluorescence immunoassay |
| Label antibody | Anti-BNP mouse monoclonal; alkaline phosphatase conjugate | Fluorescent labeled anti-BNP antibodies |
| Standard calibrator range | 0 – 4000 pg/mL | 0-5000 pg/mL |
| Limit of detection | ≤ 15 pg/mL | < 5 pg/mL |

**J. Standard/Guidance Document Referenced (if applicable):**

NCCLS EP 5-A, NCCLS EP 9-A

**K. Test Principle**

The sample and all AxSYM BNP reagents required for one test are pipetted by the Sampling Probe into various wells of a Reaction Vessel (RV). A reaction mixture is formed by combining sample and microparticles coated with Anti-BNP monoclonal antibody in the sample well of the RV. When human BNP antigen is present in the sample, it binds to the coated microparticles, forming antigen-antibody complexes on the microparticles. The monoclonal Anti-BNP:Alkaline Phosphatase Conjugate is pipetted into a second well of the RV. The BNP Wash Buffer is pipetted into a third well of the RV. The RV is immediately transferred into the Processing Center. Further pipetting is

done in the Processing Center by the Processing Probe. An aliquot of the reaction mixture, containing microparticles and bound antigen-antibody complex, is transferred to the Matrix Cell. The microparticles bind irreversibly to the glass fiber matrix. The Matrix Cell is washed to remove materials not bound to the microparticles. The Anti-BNP:Alkaline Phosphatase Conjugate is dispensed onto the Matrix Cell and it binds with the antigen-antibody complexes. The Matrix Cell is washed to remove conjugate not bound to the microparticles. The substrate, 4-Methylumbelliferyl Phosphate, is added to the Matrix Cell. The alkaline phosphatase-labeled conjugate catalyzes the removal of a phosphate group from the substrate, yielding the fluorescent product, 4-Methylumbelliferone. This fluorescent product is measured by the MEIA optical assembly.

**L. Performance Characteristics (if/when applicable):**

1. Analytical performance:
    - *a. Precision/Reproducibility:*
      In a study run according to the National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP5-A, a three-member panel was assayed in replicates of two at two separate times of the day for 20 days (n = 80 for each panel member). Testing was performed on two AxSYM Systems using a single calibration on each instrument. Within run CV(%) ranged from 4.3 to 6.3 %. Total CV(%) ranged form 6.5 to 9.4 %.
    - *b. Linearity/assay reportable range:*
      Aliquots of 8 human plasma specimens with BNP concentrations ranging from 132 to 3878 pg/mL were diluted with normal human plasma with BNP concentration > 15 pg/mL. The undiluted and diluted samples were tested in replicates of 2 using the AxSYM BNP assay. The AxSYM BNP assay demonstrated an average recovery of 100% ± 10 %.
    - *c. Traceability (controls, calibrators, or method):*
      The AxSYM BNP Standard Calibrators are traceable to an internal reference standard that has been prepared gravimetrically with synthetic BNP. The internal reference standard underwent a one-time value assignment to align with a commercially available BNP assay with a decision threshold of 100 pg/mL.
    - *d. Detection limit:*
      The AxSYM BNP assay demonstrated an analytical sensitivity of ≤ 15 pg/mL in a study where the AxSYM BNP Standard Calibrator A (0 pg/mL) was assayed multiple times (n = 12 runs in replicates of 10).
    - *e. Analytical specificity:*
      The AxSYM BNP assay was evaluated for analytical specificity in a study where cross-reactivity with human ANP, CNP, and NT-proBNP was measured by the assay. Each potential cross reactant was added to protease-inhibitor treated plasma and then assayed.

| Cross-reactant | Cross-reactant Concentration % (pg/mL) | % Cross-reactivity |
|---|---|---|
| ANP | 1000 | Not Detectable |
| CNP | 1000 | Not Detectable |
| NT-proBNP (1-46) | 1000 | Not Detectable |
| NT-proBNP (47-76) | 1000 | Not Detectable |

The AxSYM BNP assay demonstrated an average interference ≤ 10% (for each compound) in a study based upon guidance from NCCLS Protocol EP7-A. Specimens were supplemented with various drugs and potentially interfering compounds (bilirubin, hemoglobin, red blood cells, total protein, and triglycerides) at the levels indicated below.

| Drug | Drug Concentration | Drug | Drug Concentration |
|---|---|---|---|
| Acetaminophen | 30 µg/mL | Indomethacin | 36 µg/mL |
| Acetylsalicylic Acid | 600 µg/mL | Isosorbide Dinitrate | 150 ng/mL |
| Amiodarone | 6 µg/mL | Lisinopril | 4 µg/mL |
| Amlodipine besylate | 100 ng/mL | Lovastatin | 20 µg/mL |
| Ampicillin | 53 µg/mL | Methyldopa | 15 µg/mL |
| Ascorbic Acid | 40 µg/mL | Nicotine | 1 µg/mL |
| Atenolol | 10 µg/mL | Nifedipine | 400 ng/mL |
| Caffeine | 60 µg/mL | Nitrofurantoin | 4 µg/mL |
| Captopril | 5 µg/mL | Nitroglycerine | 500 ng/mL |
| Chloramphenicol | 50 µg/mL | Oxazepam | 5 µg/mL |
| Clopidogrel Bisulphate | 2.5 µg/mL | Oxytetracycline | 15 µg/mL |
| Cyclosporine | 2.5 µg/mL | Phenobarbitol | 100 µg/mL |
| Diclofenac | 50 µg/mL | Phenytoin | 50 µg/mL |
| Digoxin | 2 ng/mL | Probenecid | 600 µg/mL |
| Diltiazem | 40 µg/mL | Procainamide | 24 µg/mL |
| Dipyridamole | 80 µg/mL | Propranolol | 2 µg/mL |
| Dobutamine | 100 µg/mL | Quinidine | 12 µg/mL |
| Dopamine | 900 ng/mL | Simvastatin | 16 µg/mL |
| Enalapril Maleate | 300 ng/mL | Spironolactone | 600 ng/mL |
| Erythromycin | 60 µg/mL | Sulfamethoxazole | 400 µg/mL |
| Fenofibrate | 45 µg/mL | Trandolapril | 40 µg/mL |
| Furosemide | 60 µg/mL | Trimethoprim | 40 µg/mL |
| Heparin | 8 U/mL | Verapamil | 2 µg/mL |
| Hydralazine | 6.4 µg/mL | Warfarin | 20 µg/mL |
| Hydrochlorothiazide | 6 µg/mL | | |

| Interfering Substance | Interfering Substance Concentration |
|---|---|
| Triglycerides | 3000 mg/dL |
| Cholesterol | 500 mg/dL |
| Hemoglobin | 1000 mg/dL |
| Bilirubin | 20 mg/dL |
| Red Blood Cells | 0.4% |
| Total Protein | 12 g/dL |

*f. Assay cut-off:*

BNP results less than or equal to 100 pg/mL are representative of normal values in patients without CHF.

2. Comparison studies:
    a. *Method comparison with predicate device:*
    A Passing Bablok regression analysis between the Biosite Triage® BNP and the Abbott AxSYM BNP using 313 specimens with BNP values ranging from 0 to 3426 pg/mL, yielded a correlation coefficient of 0.956, a slope of 1.12 (95% Confidence Interval of 1.08 to 1.18) and a y-axis intercept of -8 (95% Confidence Interval of -6 to -9).
    b. *Matrix comparison:*
    EDTA plasma is the only sample type indicated.
3. Clinical studies:
    a. *Clinical sensitivity:*
    An age-matched analysis of the heart failure and non-heart failure populations was performed based on the data published by the American Heart Association in the 2000 Heart and Stroke Statistical Update and according to the age structure of the United States population. The age distributions in the intended use population are approximately as follows: individuals less than 45 years old comprise 9%,individuals 45-54 years old comprise 11%, individuals 55-64 years old comprise 22%, individuals 65-74 years old comprise 26%, and individuals 75 years and older comprise 32%. The resulting combined AUC is 0.87 (0.85 to 0.90, 95%CI). The clinical sensitivity and specificity of the AxSYM BNP assay using a decision threshold of 100 pg/mL is presented in the table below.

| | | Males (Age Group) | | | | |
|---|---|---|---|---|---|---|
| | All | <45 Years | 45-54 Years | 55-64 Years | 65-74 Years | 75+ Years |
| Sensitivity | 71.0% (328/462) | 47.1% (8/17) | 57.1% (24/42) | 57.3% (51/89) | 70.6% (115/163) | 86.1% (130/151) |
| 95% Confidence Interval | 66.6 to 75.1% | 23.0 to 72.2% | 41.0 to 72.3% | 46.4 to 67.7% | 62.9 to 77.4% | 79.5 to 91.2% |
| Specificity | 94.8% (403/425) | 97.2% (104/107) | 100.0% (71/71) | 97.9% (92/94) | 88.7% (102/115) | 89.5% (34/38) |
| 95% Confidence Interval | 92.3 to 96.7% | 92.0 to 99.4% | 94.9 to 100.0% | 92.5 to 99.7% | 81.5 to 93.8% | 75.2 to 97.1% |

| | | Females (Age Group) | | | | |
|---|---|---|---|---|---|---|
| | All | <45 Years | 45-54 Years | 55-64 Years | 65-74 Years | 75+ Years |
| Sensitivity | 80.5% (186/231) | 44.4% (4/9) | 73.3% (11/15) | 50.0% (13/26) | 80.6% (58/72) | 91.7% (100/109) |
| 95% Confidence Interval | 74.8 to 85.4% | 13.7 to 78.8% | 44.9 to 92.2% | 29.9 to 70.1% | 69.5 to 88.9% | 84.9 to 96.2% |
| Specificity | 88.4% (411/465) | 95.9% (94/98) | 90.7% (68/75) | 89.6% (69/77) | 85.7% (114/133) | 80.5% (66/82) |
| 95% Confidence Interval | 85.1 to 91.2% | 89.9 to 98.9% | 81.7 to 96.2% | 80.6 to 95.4% | 78.6 to 91.2% | 70.3 to 88.4% |

*b. Clinical specificity:*
See above

*c. Other clinical supportive data (when a and b are not applicable.*

4. Clinical cut-off:
Data from the clinical studies were used to generate The Receiver Operating Characteristic (ROC) curve of BNP decision thresholds versus clinical sensitivity and clinical specificity. At a decision threshold of 100 pg/mL, the BNP assay demonstrated a clinical sensitivity and specificity of 74.2% and 91.5% respectively. The area under the curve is 0.90 (0.86 to 0.92, 95% CI).
5. Expected values/Reference range:
Plasma samples from 890 individuals (465 females, 425 males) who had not been diagnosed with heart failure were tested. This population included non-hospitalized patients with renal disease (not on dialysis), diabetes, hypertension and chronic obstructive pulmonary disease. BNP levels for these patients were not statistically different from the population of apparently healthy individuals. The data are summarized below.

**Non-Heart Failure Population - All (Age Group)**

| | All | <45 Years | 45-54 Years | 55-64 Years | 65-74 Years | 75+ Years |
|---|---|---|---|---|---|---|
| Sample Size (N=) | 890 | 205 | 146 | 171 | 248 | 120 |
| Median (pg/mL) | 21 | 17 | 9 | 24 | 23 | 31 |
| Mean (pg/mL) | 39 | 28 | 21 | 37 | 47 | 63 |
| SD (pg/mL) | 66 | 36 | 30 | 48 | 80 | 109 |
| 95th Percentile | 135 | 85 | 87 | 119 | 160 | 254 |
| Percentage < 100 pg/mL | 91.5% | 96.6% | 95.2% | 94.2% | 87.1% | 83.3% |
| Minimum (pg/mL) | 0 | 0 | 0 | 0 | 0 | 0 |
| Maximum (pg/mL) | 907 | 263 | 142 | 380 | 907 | 837 |

**Non-Heart Failure Population - Males (Age Group)**

| | All | <45 Years | 45-54 Years | 55-64 Years | 65-74 Years | 75+ Years |
|---|---|---|---|---|---|---|
| Sample Size (N=) | 425 | 107 | 71 | 94 | 115 | 38 |
| Median (pg/mL) | 14 | 12 | 1 | 17 | 21 | 37 |
| Mean (pg/mL) | 30 | 23 | 9 | 26 | 47 | 49 |
| SD (pg/mL) | 61 | 34 | 14 | 45 | 96 | 51 |
| 95th Percentile | 104 | 73 | 40 | 80 | 150 | 121 |
| Percentage < 100 pg/mL | 94.8% | 97.2% | 100.0% | 97.9% | 88.7% | 89.5% |
| Minimum (pg/mL) | 0 | 0 | 0 | 0 | 0 | 0 |
| Maximum (pg/mL) | 907 | 200 | 57 | 380 | 907 | 254 |

**Non-Heart Failure Population - Males (Age Group)**

| | All | <45 Years | 45-54 Years | 55-64 Years | 65-74 Years | 75+ Years |
|---|---|---|---|---|---|---|
| Sample Size (N=) | 465 | 98 | 75 | 77 | 133 | 82 |
| Median (pg/mL) | 26 | 23 | 23 | 37 | 23 | 25 |
| Mean (pg/mL) | 46 | 34 | 34 | 51 | 46 | 69 |
| SD (pg/mL) | 70 | 37 | 36 | 48 | 63 | 126 |
| 95th Percentile | 150 | 89 | 111 | 155 | 159 | 266 |
| Percentage < 100 pg/mL | 88.4% | 95.9% | 90.7% | 89.6% | 85.7% | 80.5% |
| Minimum (pg/mL) | 0 | 0 | 0 | 0 | 0 | 0 |
| Maximum (pg/mL) | 837 | 263 | 142 | 230 | 374 | 837 |

Plasma samples from 693 patients with diagnosed heart failure (231 females, 462 males) were tested with the AxSYM BNP assay. All patients in this population were categorized according to the functional classification system published by the New York Heart Association (NYHA). This system divides heart failure patients into one of four categories of increasing disease progression (classes I to IV) based upon a subjective assessment of the patient's clinical signs and symptoms. The data from this study are summarized below.

**Heart Failure Population - All**

| | | NYHA Functional Class | | | |
|---|---|---|---|---|---|
| | All | I | II | III | IV |
| Sample Size (N=) | 693 | 124 | 319 | 190 | 60 |
| Median (pg/mL) | 298 | 133 | 266 | 335 | 1531 |
| Mean (pg/mL) | 578 | 320 | 432 | 656 | 1635 |
| SD (pg/mL) | 771 | 388 | 574 | 841 | 1097 |
| 5th Percentile | 14 | 9 | 15 | 12 | 188 |
| 95th Percentile | 2154 | 1257 | 1534 | 2516 | >4000 |
| Percentage ≥ 100 pg/mL | 74.2% | 58.1% | 73.0% | 79.0% | 98.3% |
| Minimum (pg/mL) | 0 | 3 | 0 | 0 | 14 |
| Maximum (pg/mL) | >4000 | 1651 | >4000 | >4000 | >4000 |

**Heart Failure Population - Males**

| | | NYHA Functional Class | | | |
|---|---|---|---|---|---|
| | All | I | II | III | IV |
| Sample Size (N=) | 462 | 94 | 215 | 121 | 32 |
| Median (pg/mL) | 268 | 122 | 258 | 293 | 1645 |
| Mean (pg/mL) | 524 | 314 | 409 | 597 | 1646 |
| SD (pg/mL) | 719 | 390 | 539 | 821 | 1032 |
| 5th Percentile | 12 | 9 | 14 | 22 | 265 |
| 95th Percentile | 1976 | 1281 | 1356 | 2288 | 3654 |
| Percentage ≥ 100 pg/mL | 71.0% | 56.4% | 70.7% | 76.0% | 96.9% |
| Minimum (pg/mL) | 0 | 3 | 0 | 0 | 14 |
| Maximum (pg/mL) | >4000 | 1408 | 3782 | >4000 | >4000 |

**Heart Failure Population - Females**

| | | NYHA Functional Class | | | |
|---|---|---|---|---|---|
| | All | I | II | III | IV |
| Sample Size (N=) | 231 | 30 | 104 | 69 | 28 |
| Median (pg/mL) | 385 | 174 | 298 | 466 | 1408 |
| Mean (pg/mL) | 685 | 341 | 481 | 760 | 1623 |
| SD (pg/mL) | 858 | 388 | 641 | 870 | 1186 |
| 5th Percentile | 16 | 14 | 21 | 12 | 244 |
| 95th Percentile | 2593 | 1022 | 2031 | 2718 | >4000 |
| Percentage ≥ 100 pg/mL | 80.5% | 63.3% | 77.9% | 84.1% | 100.0% |
| Minimum (pg/mL) | 0 | 10 | 0 | 0 | 173 |
| Maximum (pg/mL) | >4000 | 1651 | >4000 | >4000 | >4000 |

## M. Conclusion:

Based upon a review of the information presented in this submission, I recommend that this device is substantially equivalent to devices regulated by 862.1117 B-type natriuretic peptide test system; 862.1150, Calibrator, Secondary; 862.1660, Single (specified) analyte controls (assayed and unassayed).